REMARKS

Applicants thank the Examiner for the review of the instant application. Claims 6-8 and 11-17 remain pending and are presented for further examination. For the reasons stated below, Applicants respectfully traverse the rejection of the pending claims.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of Claims 6-8 and 11-17 under 35 U.S.C. § 101 as lacking a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Actions. The PTO asserts that one skilled in the art would not know how to use the claimed invention. According to the PTO, "the specification provides data showing an indeterminate increase in mRNA in one normal tissue.... However, there is no evidence regarding whether or not PRO1270 polypeptide levels are also increased ...." *Office Action* at 3. The PTO continues to rely on Pennica *et al.*, Haynes *et al.*, and Hu *et al.*, for the propositions that what is often seen is a lack of correlation between mRNA levels and increased peptide levels, that polypeptide levels cannot be accurately predicted from mRNA levels, and that the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels. *Office Action* at 3. The PTO argues that further research is required to determine whether the PRO1270 polypeptide is differentially expressed, making the asserted utility not substantial.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the Examiner has not met the PTO's burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However, even if the Examiner has met the PTO's initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated previously, Applicants' evidence need not

be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants remind the PTO that the asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1270 polypeptide is expressed at least two-fold higher in normal lung tissue compared to lung tumor tissue;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding change in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the mRNA for the PRO1270 polypeptide is differentially expressed in lung tumor tissue compared to normal lung tissue, it is more likely than not that the PRO1270 polypeptide is likewise differentially expressed in these tumors; the PRO1270 polypeptide is therefore useful as a diagnostic tool to distinguish lung tumor tissue from normal lung tissue.

Applicant's maintain that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

The PTO has Concluded that the data in Example 18 are Sufficient to Establish the Utility of the Claimed Invention

As an initial matter, Applicants point out that in other applications filed by Applicants that rely *on data from the exact same disclosure, Example 18*, and in which Applicants have submitted *substantially the same references* in support of their asserted utility, the PTO has concluded that: "[b]ased on the totality of evidence of record, **one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels,** absent evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of nucleic acids encoding PRO1180, also supports a conclusion of differential expression of PRO1180 polypeptide. Therefore, one of ordinary skill in the art would be able to use the

PRO1180 polypeptide diagnostically for distinguishing normal kidney and rectal tumor tissues compared to kidney tumor and normal rectal tissue, as asserted by Applicant." See *Examiners Reasons for Allowance* in pending Application No. 10/063,529. See also *Examiners Reasons for Allowance* in Application No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583, all of which conclude that the data presented in Example 18, which demonstrate differential expression of the nucleic acids encoding certain PRO polypeptides, also support a conclusion of differential expression of the PRO polypeptides, making the claimed PRO polypeptides and antibodies that bind the PRO polypeptides useful for diagnostic purposes.

Applicants therefore request that the Examiner recognize the utility of the claimed invention, supported by the data presented in Example 18 and Applicants numerous cited references, as was done in the other applications referenced above.

The Previously Cited References Provide Evidence that Changes in mRNA Levels are Correlated with Changes in Protein Levels

Applicants incorporate by reference their previously submitted arguments in regard to Hu *et al.* and will not reiterate those arguments here. However, Applicants will once again explain why the PTO's reliance on Hu is misplaced. Hu bases his conclusions on data generated from high throughput microarrays:

> In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study. *Hu* at 405, left column, first paragraph (emphasis added).

As Applicants previously pointed out, Applicants are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis. Applicants submitted a reference by Kuo *et al.*, (Proteomics 5(4):894-906 (2005)), in which the authors state that PCR is a "more reliable and sensitive" than microarray technology. *Kuo et al.* at Abstract (emphasis added). Thus, even if accurate, Hu's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

Applicants maintain that Kuo supports their assertion that Applicants' PCR data are more accurate and reliable than the microarray data relied on by Hu. Because PCR is more accurate and reliable than microarrays, conclusions regarding the relevance of mRNA transcript changes based on microarray data, such as those set forth in Hu, are not applicable to data generated using

the more reliable method. Kuo supports this assertion because it is evidence that one of skill in the art would regard PCR as a more accurate and reliable method of assessing changes in mRNA.

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1270 polypeptide in lung tumors, it is likely that the PRO1270 polypeptide is likewise differentially expressed in these tumors; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

The PTO's cited references are not contrary to Applicants' asserted utility

In response to Applicants' arguments, the PTO continues to rely on Pennica, Haynes, and Feroze-Merzoug as support for its argument that mRNA levels are not predictive of protein levels. Applicants have discussed at length in previous responses why these references are not relevant to the issue of whether changes in mRNA level for a particular gene leads to changes in protein level. Applicants will not repeat their arguments here.

Applicants note, however, that the PTO seems to have misinterpreted the data presented in the present application. On page 8 of the Office Action, the PTO states: "It is hard to conceive of a specific and substantial utility for a protein for which so little data or information is given. For example, why were other tissues not tested, as was the case for other PRO polypeptides?"

Example 18 of the specification clearly states that oligonucleotide probes constructed from the PRO polypeptide encoding nucleotide sequences "were employed in standard quantitative PCR amplification reactions with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a quantitative determination of the level of expression of the PRO-polypeptide encoding nucleic acid in the various tumor and normal tissues tested." Thus, each of the probes was tested against a full range of normal and cancerous tissue types – the results listed in Example 18 merely report the tissues where differential expression was detected. In this case, Example 18 shows that the PRO1270 mRNA was differentially expressed in lung tumors. The PTO has no basis for questioning "why were other tissues not tested, as was the case for other PRO

polypeptides?" as all PRO polypeptides were tested for differential expression in the same way using the same tissue types.

Previously Submitted Exhibits 2-13 Are Relevant to the PTO's Argument Against Allowance of the Claims

Applicants continue to assert that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1270 polypeptide in lung tumors, it is more likely than not that the PRO1270 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors, and antibodies that bind such proteins, have utility as diagnostic tools.

Applicants previously submitted Exhibits 2-13, comprising 81 references, in support of their argument for the correlation between mRNA levels and protein levels. The PTO fails to address these references in any way. Applicants maintain that the overwhelming evidence they have provided strongly supports Applicants' position.

In addition, Applicants have previously submitted the Polakis Declaration in support of their position that in general, changes in mRNA levels correlate with changes in protein levels. Applicants submit herewith as Exhibit 1 a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions.

Applicants also submit herewith a copy of a declaration by Randy Scott, Ph.D. (attached as Exhibit 2). Dr. Scott is an independent expert in the field of molecular diagnostics, with over 15 years experience. He is the author of over 40 scientific publications in the fields of protein biology,

gene discovery, and cancer, and is inventor on several issued patents. His curriculum vitae is attached to the declaration. In paragraph 10 of his declaration, Dr. Scott states:

> One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels. *Scott Declaration* at ¶10 (emphasis added).

Applicants submit the opinion of yet another expert in the field that changes in mRNA level for a particular protein in a given tissue generally lead to a corresponding change in the level of the encoded protein. Importantly, Dr. Scott also states that, contrary to the contentions of the PTO, diagnostic markers can be identified "without the need to directly measure individual protein expression levels." This opinion is supported by Dr. Scott's extensive experience in the field, as well as the fact that an entire industry has developed around technology used to assess differential mRNA expression. As stated previously, there would be little reason to study changes in mRNA expression levels if those changes did not result in corresponding changes in the encoded protein levels.

The case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." *Id.* at 1583. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a

disagreement over the significance or meaning of the facts offered." Part IIB, 66 Fed. Reg. 1098 (2001).

In summary, Applicants have submitted herewith two additional expert Declarations in addition to the declarations and over 115 references already of record, which support Applicants' asserted utility, either directly or indirectly. This evidence overwhelmingly supports the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions. However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

The PTO's Position is Inconsistent with the Utility Guidelines and the Courts

In response to Applicants' evidence and arguments, the PTO takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed polypeptides – specifically, direct evidence of differential expression of PRO1270 polypeptide in tumor and normal tissue. Applicants submit that this requirement is inconsistent with the Utility Guidelines and the courts.

Adopting the PTO's standard for utility would result in a per se rule that a difference in mRNA expression cannot establish a utility for the encoded polypeptide and antibodies thereto. Thus, the PTO chooses to heighten the utility requirement to require specific, direct evidence of utility when there are exceptions to a generally accepted rule that is relied upon for utility. This heightened utility requirement is inconsistent with the Utility Guidelines and the courts. There is no requirement that utility be dispositively proven:

> Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) ... Instead, evidence will be

> sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

There is no requirement that only direct evidence of utility is sufficient to establish utility. Instead, it is established that indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101. *Nelson v. Bowler*, 626 F.2d 853, 856. Furthermore, there is no requirement that indirect evidence necessarily and always prove actual utility. Instead, there only need be a reasonable correlation between the indirect evidence and the asserted utility. *Id.* at 857, *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051. The indirect evidence need not absolutely prove the asserted utility. All that is required is that the tests be reasonably indicative of the asserted utility. In other words, there need only be a sufficient correlation between the indirect evidence and the utility so as to convince those skilled in the art, to a reasonable probability, that the novel compound will possess the asserted utility. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564.

In the present case, Applicants submit that their evidence (differential mRNA expression) is reasonably linked to the asserted utility (diagnostic use of the encoded polypeptide). Insofar as it is uncontested that differential mRNA expression is reasonably linked to differential polypeptide expression, Applicants submit that such linkage is sufficient to fulfill the requirements of 35 U.S.C. §101 as provided by the guidance of the Utility Guidelines and the courts.

In conclusion, the PTO's heightened requirement for establishing utility of the presently claimed polypeptides is contrary to the Utility Guidelines and the courts: it is sufficient to present evidence of differential mRNA expression since it is understood in the art that differential mRNA expression is reasonably linked to differential polypeptide expression. As discussed above, even if the PTO has presented evidence that changes in mRNA expression is not always correlated with changes in protein expression, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level typically lead to corresponding changes in protein level. As such, Applicants have established that it is more likely than not that one of skill in the art would believe that because the PRO1270 mRNA is differentially expressed in lung tumors as compared to normal lung tissue, the PRO1270 polypeptide will likewise be

differentially expressed in these tumors. Accordingly, when the evidence is applied to the proper standard for utility, it is clear that this differential expression of the PRO1270 polypeptides establishes their utility as diagnostic tools for cancer, particularly lung tumor. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Conclusion

The PTO has asserted that the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels. Applicants have addressed each of the PTO's supporting references and shown that they are either irrelevant, or taken as a whole, actually support Applicants' assertion that a change in mRNA level leads to a corresponding change in the level of the encoded protein. In addition, Applicants have submitted expert declarations, textbook excerpts, and over 115 scientific publications which support Applicants' asserted utility.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing **some** beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely... A commercially successful product is not required... Nor is it essential that the invention accomplish all its intended functions... or operate under all conditions... partial success being sufficient to demonstrate patentable utility... In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed PRO1327 polypeptides set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO maintains its rejection of Claims 6-8 and 11-17 as lacking enablement. The PTO states that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants respectfully request that to the extent the enablement rejection is based on a lack of utility, the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Rejections under 35 U.S.C. § 112, first paragraph – Written Description

The PTO rejects Claims 14 and 15 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. The PTO maintains that Applicants were not in possession of all or a significant number of polypeptides that have 95-99% homology to SEQ ID NO:88 while retaining the function of SEQ ID NO:88. The PTO argues that "[t]here is no discussion in the instant disclosure about the structure of PRO1270, nor about related molecules, such that molecules that vary as much as 5% from PRO1270 could be evaluated for similarity of function." *Office Action* at 9.

The PTO has Failed to Meet Its Initial Burden of Rebutting the Presumption that the Pending Claims are Adequately Described

To overcome the presumption that the claimed subject matter is adequately described, the PTO must present "evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 U.S.P.Q. at 97." *M.P.E.P.* § 2163.04. To support its rejection of pending Claims 14 and 15, the PTO relies on the arguments that the claims lack a functional limitation, and that "even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of

encompassed PRO1270 polypeptides, and therefore, would not know how to make or use them." *Office Action* at 11.

The PTO has not provided more than conclusory statements as to why one of skill in the art would not recognize a description of the claimed invention in Applicants' disclosure. First, the claims clearly have a functional limitation, as being able to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:88 in lung tissue samples is clearly a function that is dependent on the structure of the polypeptide. Second, the claimed polypeptides do not differ significantly from the disclosed SEQ ID NO:88 for the reasons discussed below, and the PTO has made no more than a conclusory statement to the contrary. The PTO has failed to rebut the presumption that the specification satisfies the written description requirement for Claims 14-15. *See M.P.E.P.* § 2163.04.

Rejected Claims 14 and 15 are Adequately Described

The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991) (emphasis added). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

Claims 14-15 are adequately described by the specification. These claims are directed to an isolated polypeptide having at least 95% amino acid sequence identity to the recited polypeptide sequences, wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:88 in lung tissue samples.

Applicants maintain that there is no substantial variation within the species which fall within the scope of the rejected claims, which require at least 95% amino acid sequence identity to SEQ ID NO:88 and can be used to generate antibodies which specifically detect the polypeptide of SEQ ID NO:88 in lung tissue samples. As such, Applicants were in possession of the common attributes or features of the claimed subject matter.

The rejected claims are analogous to the claims discussed in Example 14 of the written description training materials available on the PTO's website. In Example 14, the written description requirement was found to be satisfied for claims directed to polypeptides with 95% homology to a disclosed sequence that also possess a recited catalytic activity, where procedures for making variant proteins were routine in the art and the specification provided an assay for detecting the recited catalytic activity of the protein. This disclosure satisfies the written description requirement even though the applicant had disclosed only a single species and had not made any variants. The Guidelines state that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity."

Similarly, the pending claims also have at least 95% or 99% sequence identity to the disclosed sequence, and must be able to generate antibodies which specifically detect the polypeptide of SEQ ID NO:88 in lung tissue samples. As in Example 14, at the time of the effective filing date of the instant application, it was well known in the art how to make polypeptides with at least 95% or 99% amino acid sequence identity to the disclosed sequences. *See, e.g., Specification* at ¶¶ [0256]-[0271]. In addition, the specification discloses in detail how to make antibodies which specifically detect a particular PRO polypeptide, and how to use them to detect the PRO polypeptide in a particular tissue. *See, e.g., Specification* ¶¶ [0363]-[0379], [0407], and [0493]-[0499]. Like a particular catalytic activity, the function of being useful to produce an antibody specific to SEQ ID NO:88 is directly related to the structure of the claimed polypeptides. Thus, like Example 14, the genus of polypeptides that have at least 95% amino acid sequence identity to the disclosed sequences and possess the described functional activity are adequately described.

Claims 16 and 17, drawn to particular embodiments of Claim 14, are also fully described by the specification. The PTO does not contest the written description support for any embodiment recited in Claims 16-17.

Applicants submit that the applicability of Example 14 is not limited to polypeptides for which the biological function is known and recited, but extends to all situations where the

polypeptide is useful and there is no substantial variation within the species encompassed by the claims. The purpose of the recited catalytic activity in the example is to limit the amount of structural variation within the species. The commentary in the Guidelines states that the description of an assay to detect variants which have the recited activity, along with 95% homology, is sufficient to satisfy the written description requirement.

Similarly, in the instant case, Claims 14-17 must share a particular "biological activity" which restricts the amount of permissible structural variation within the species – the claimed polypeptides must be useable to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:88 in lung tissue samples. This limitation combined with the disclosure of how to make and test the recited antibodies generated from the claimed polypeptides, along with the requirement of least 95% or 99% amino acid sequence identity, results in claimed subject matter where there is no substantial variation within the species encompassed by the claims. Accordingly, Applicants maintain that the pending claims are analogous to the claims in Example 14.

As for the PTO's conclusory and unsupported statement that "even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of encompassed PRO1270 polypeptides, and therefore, would not know how to make and use them," the basic premise that a large genus can not be adequately described by a single species is simply wrong. As pointed out previously, in a recent Federal Circuit decision, *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

> [W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious. ... A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants.
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> ***

> Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

The Court did not require the applicants in *Wallach* to actually make or individually describe all of the vast number of sequences which encode the disclosed sequence. This is in spite of the fact that only a single sequence was disclosed, and the encompassed genus was enormous due to codon degeneracy in the genetic code – even the most skilled artisan could not individually envision the detailed chemical structure of the nucleic acids encompassed by the claimed genus. The Court reasoned that because it is routine to convert between amino acid sequences to nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to place the applicants in possession of the enormous genus of nucleic acids which could encode the sequence.

The facts in *Wallach* are very similar to the instant case. Here, Applicants have disclosed SEQ ID NO:88, and claim polypeptides which are at least 95% identical to it and have the functional limitation of the ability to generate antibodies which can be used to specifically detect SEQ ID NO:88in lung tissue samples. As discussed above, it is routine in the art to create polypeptides which have at least 95% sequence identity to SEQ ID NO:88 – it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence. Similarly, it is well within the knowledge of those skilled in the art how to determine which polypeptides can be used to make the recited antibodies. The predictability of this structure/function combination is sufficient to place the claimed subject matter in the possession of the Applicants, and thus the claimed polypeptides are adequately described. The *Wallach* opinion makes clear that there is no need to literally describe more than a single species to adequately describe a large genus where one of skill in the art recognizes that the disclosed species puts the applicant in possession of the claimed genus.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:88, by specifying a high level of amino acid sequence identity, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the

species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept. 28, 2006

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